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Juvenile-onset mixed connective tissue disease associated with macrophage activation syndrome: A case with refractory Raynaud's phenomenon

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ABSTRACT

Introduction: Mixed connective tissue disease (MCTD) is an autoimmune disease that is rare in children. The disease is presented with complex clinical features, so early diagnosis is challenging. Herein we describe the management and outcome of a girl with MCTD associated with macrophage activation syndrome (MAS) and refractory Raynauds' phenomenon.

Case report: A 13-year-old girl was admitted to the pediatric rheumatology ward with mild fever, reduced appetite, 6 kg weight loss (body mass index 15.8), digital ulcers, sclerodactyly, scleroderma, dysphagia, gastroesophageal reflux and arthralgia. She also had photosensitivity, Raynaud's phenomenon, painless oral ulcers, and malar rash. She developed arthritis of the knees and ankles with limited range of motion. Spirometry showed a restrictive pattern. There was speckled antinuclear antibodies (ANA; 1/1260) and positive β-2-glycoprotein, U1-ribonucleoprotein (U1-RNP), anti-Scl-70 and anti-Ro52 antibodies. Anti-double stranded deoxyribonucleic acid and anti-cyclic citrullinated protein antibodies were negative. Based on clinical and laboratory findings, MCTD was confirmed. The child was treated with steroid, vasodilators, and immunosuppressives. She had an attack of salmon pink rashes, spiky fevers, Koebner phenomenon, serositis, and organomegaly and the diagnosis of associated MAS was held. The patient was treated with pentoxifylline, prednisolone, methotrexate, low dose aspirin, nifedipine, and hydroxychloroquine. On follow up there was refractory digital ulcers and Raynaud's phenomenon; transthoracic endoscopic sympathectomy was performed and digital ulcers and coldness resolved.

Conclusion: MCTD may present with a myriad of rheumatic manifestations and in association with MAS the diagnosis and management may be challenging. Refractory Raynauds' phenomenon may remarkably improve on transthoracic sympathectomy.

1. Introduction

Juvenile mixed connective tissue disease (MCTD) is a rare autoimmune disease characterized by various overlapping features such as juvenile idiopathic arthritis (JIA), polymyositis, cutaneous scleroderma, systemic lupus erythematosus (SLE), and systemic sclerosis (SSc) [1,2]. Fatigue, mild fever, cold fingers, paresthesias, puffiness of the hands and fingers, arthritis, myositis, and skin rash are main features of the disease [3]. The heart, lungs, and kidneys can also be affected in the later stages of the disease [4]. MCTD is an autoimmune disease with unknown underlying mechanism, yet genetic factors may play a key role in its etiology [5]. Additionally, certain viruses and chemicals may also contribute. It is noteworthy that MCTD is very rare in children [6]. The disease presents with features of more than one, usually two, connective tissue diseases. Herein, we describe a 13-year-oldgirl admitted to hospital with sequential complaints and findings compatible with features of four rheumatologic disorders: SSc, SLE, JIA, and macrophage activation syndrome (MAS) which eventually, lead to the final diagnosis of MCTD.

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2. Case report

A 13-year-old girl was admitted to the pediatric rheumatologic ward, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran with arthralgia of the knees and wrists with back pain for 2 weeks duration and mild fever for 2 days. She also complained of reduced appetite, 6 kg weight loss (weight: 40 kg; height: 150 cm; and BMI: 15.8 kg/m^2), gastroesophageal reflux, and upper painless dysphagia to solids, as well as coldness, pain and peripheral cyanosis of fingers following contact with water and cold weather from 2 months ago. Also, she complained of muscle weakness. On physical examination, she had restricted active and passive range of motion (ROM) of the knees and ankles, swelling and warmness of the joints (arthritis), sclerodactyly, and digital ulcers, as well as tenderness of sacroiliac joints. The Patrick's test for Flexion, ABduction, and External Rotation (FABER) test was also positive. She also had malar rash, photosensitivity, Raynaud's phenomenon, and painless oral ulcers. The muscle power of the upper and lower extremities was normal. The informed consent has been obtained from parents of the girl.

Complete blood count (CBC) showed a white blood cell count of $5200 \times 10^3/mm^3$ with absolute lymphopenia ($624 \times 10^3/mm^3$). The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Immunoglobulins (Ig_s), muscle enzymes and complements level were within normal limits. Serological tests for hepatitis, infectious mononucleosis, cytomegalovirus (CMV), and parvovirus B19 were negative. Antinuclear antibodies (ANA) were highly positive (ANA:1/1260) with speckled pattern. U1-ribonucleoprotein autoantibody (U1-RNP) was increased (3^+). The anti-double stranded deoxyribonucleic acid (anti-ds-DNA) and also anti-cyclic citrullinated protein antibodies (anti-CCP) were negative. β-2-glycoprotein (β-2GP) antibodies (IgM and IgG) were three times more than normal concentration. Topoisomerase I (Scl-70) and anti Ro antibodies (Ro52) had been increased (2^+ and >200 U/ml respectively).

Her chest X-ray, echocardiography, abdominal and pelvic ultrasound were normal. Lung high-resolution computed tomography (HRCT) was normal; however, a restrictive pattern was observed in her lung on Spirometry test analysis. Bone mineral densitometry revealed low bone mineral content (with Z score −3.3). MCTD was eventually diagnosed according to the increased levels of ANA, β-2GP antibodies, U1-RNP, Scl-70 and Ro52, as well as the presence of SSc and SLE according to the classification and diagnostic criteria [7].

The patient had received prednisolone (0.5 mg/kg/day), methotrexate (MTX) (10 mg/m^2/w), hydroxychloroquine (HCQ) (6 mg/kg/day), naproxen (15 mg/kg/ day) and nifedipine (0.25 mg/kg/day). Pamidronate (1 mg/kg/day) was also infused for 3 days every three months. On monthly follow-up, arthritis was resolved after 3 months. Furthermore, photosensitivity was resolved. Malar rash and oral ulcers were negative and her weight had been increased by 2 kg after 3 months. At the end of 4th month, the patient developed deep pain on the right hand from fingers tip to the clavicle besides digital ulcers and puffiness. Then she was admitted to hospital and started treatment with alprostadil (10 mg/kg/day for 5 days) and heparin. Furthermore, she received rituximab (500 mg/m^2/day) two times biweekly. After discharge, pentoxifylline, antiplatelet dose of acetylsalicylic acid (ASA) and warfarin were added.

Three months later, the case was re-admitted with high-grade fever, headache, vomiting and lethargy. Laboratory investigations revealed leukocytosis, neutrophilia, and increased levels of ESR and CRP. Lumbar puncture (LP) was performed to examine the cerebrospinal fluid (CSF) analysis and revealed a normal result. CSF and blood cultures, urinalysis, and viral serologic markers were also negative. Chest x-ray, echocardiography, abdominal and pelvic ultrasound results were normal. During hospitalization, she developed high fever spikes (>39 °C) along with the salmon-colored rash. Koebner's phenomenon was positive. On the 5th day after admission, the patient presented respiratory distress and pulmonary hemorrhage. She also had persistent fever, hepatosplenomegaly, serositis, cytopenia and a normal ESR.

The patient was then transferred to pediatric intensive care unit (PICU) and received intravenous immunoglobulin (2 g/kg over 12 h), pulse methylprednisolone (30 mg/kg/day for three days), and intravenous cyclophosphamide (CYC) (500 mg/m^2) being diagnosed as systemic-onset JIA with macrophage activation syndrome (MAS) according to international league against rheumatism (ILAR) criteria for systemic JIA as well as the 2016 classification guidelines for MAS complicating systemic JIA [8,9]. Elevated liver enzymes, high triglycerides, hypofibrinogenemia, and the marked increased serum ferritin level (6500 ng/ml) were revealed two days later. Treatment with pentoxifylline, prednisolone, MTX, ASA, nifedipine, and HCQ was also continued. Intravenous pulse CYC (500 mg/m^2) was continued till 6 months and then every 3 months. During these periods, she developed fingers wounds several times and also complained from pain and peripheral cyanosis of fingers; refractory Raynaud's phenomenon. A right side transthoracic endoscopic sympathectomy was performed which showed a good response. Ten months later the same surgery was also done for left side and the patient ulcers and coldness significantly resolved.

3. Discussion

A 13-year-old girl with MCTD presenting by multiple manifestations including muscle weakness, fever, Raynaud's phenomenon and arthritis has been reported. She had also malar rash, photosensitivity and painless oral ulcers and gradually developed manifestations of systemic JIA and MAS. Increased levels of β-2GP antibodies, Scl-70, Ro52, ANA, and U1-RNP pointed to the possible diagnosis of systemic-onset JIA, SSc and SLE making the MCTD a potentially challenging diagnosis as the manifestations usually occur sequentially over time. The common features of other rheumatic diseases add to the difficulty in defining the disease. The patient was diagnosed as a case of MCTD in line with the various classification criteria [7,10]. Although MCTD occurs worldwide and affects people of all ages, it is rare in children [1,2]. Several studies reported MCTD in children [11–15]. *Yang et al.* reported two girls (10- and 13-year-old) with MCTD initially presenting with JIA, muscle weakness, Raynaud's, elevated creatine kinase and liver enzymes, sclerodactyly, arthralgia, lymphadenopathy, pericardial effusion, and paralytic ileus. Both had high serum titers of ANA and were seropositive for anti-RNP [16]. In another study, *Latuśkiewicz-Potemska et al* reported a 10-year-old girl with MCTD presented with sclerodactyly and trophic damages of fingers accompanied by Raynaud's [14]. High levels of ANA and U1-RNP, which present in most MCTD patients, were found reliable tests for the diagnosis of the disease [2]. Nevertheless, these antibodies may present in healthy people and in other disorders.

Treatment of MCTD is similar to that of SLE, autoimmune myositis, and SSc; however, it depends on the severity of disease symptoms. Some patients require continuous treatment, while others need treatment only during periods of heightened disease activity. Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, HCQ, and immunosuppressive drugs (e.g. MTX and azathioprine) are usually used for these patients [5]. Immunosuppressive drugs are usually used in moderate to severe cases.

Several studies have shown the beneficial effect of sympathectomy in patients with Raynaud's phenomenon [17–19]. MTX and CYC have been used as immunosuppressives in the present case. She received maintenance treatment with pentoxifylline, prednisolone, MTX, ASA, nifedipine, pulse CYC, and HCQ. However, after treatment with these drugs, she still suffered with a refractory Raynaud's phenomenon. Eventually, right and left hands transthoracic endoscopic sympathectomy was performed and the patient's symptoms resolved. The role of sympathectomy in refractory Raynaud's phenomenon in adolescents has been reported [19]. Different approaches have been used including local (digital or wrist block) or regional (cervical or lumbar) chemical, localized digital microsurgery and transthoracic endoscopic sympathectomy [18,20]. Sympathectomy should be reserved for patients with refractory digital ischemia and ulcers.

In conclusion, MCTD may present with a myriad of rheumatic manifestations and in association with MAS the diagnosis and management may be challenging. Refractory Raynauds' phenomenon may remarkably improve on transthoracic sympathectomy.

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Conflict of interest

The authors declare no conflict of interest.

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